Solu-Medrol

1. NAME OF THE MEDICINAL PRODUCT

Solu-Medrol Act-O-Vial 40 mg Powder and solvent for solution for injection
Solu-Medrol 500 mg Powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The active ingredient of Solu-Medrol is methylprednisolone. It is present in the form of methylprednisolone sodium succinate.

Solution for injection: Act-O-Vial system:
Solu-Medrol 40 mg Powder and solvent for solution for injection: each vial contains methylprednisolone sodium succinate equivalent to 40 mg methylprednisolone

Powder and solvent for solution for injection:
Solu-Medrol 500 mg Powder and solvent for solution for injection: each vial contains methylprednisolone sodium succinate equivalent to 500 mg methylprednisolone

3. PHARMACEUTICAL FORM

Each package contains a sterile powder for injection and a sterile solution.
Intravenous and intramuscular administration.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Glucocorticoids should only be considered as a purely symptomatic treatment, unless in case of some endocrine disorders, where they are used as substitution treatment.

Anti-inflammatory treatment

- *Rheumatic disorders*

As adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in:

- Post-traumatic osteoarthritis
- Synovitis of osteoarthritis
- Rheumatoid arthritis, including juvenile rheumatoid arthritis (selected cases may require low-dose maintenance therapy)
- Acute and subacute bursitis
- Epicondylitis
- Acute non-specific tenosynovitis
- Acute gouty arthritis
- Psoriatic arthritis
- Ankylosing spondylitis

- *Collagen diseases (immune complex diseases)*

During an exacerbation or as maintenance therapy in selected cases of:

- Systemic lupus erythematosus (and lupus nephritis)
- Acute rheumatic carditis
- Systemic dermatomyositis (polymyositis)

- Polyarteritis nodosa
- Goodpasture's syndrome

- *Dermatologic diseases*
- Pemphigus
- Severe erythema multiforme (Stevens-Johnson syndrome)
- Exfoliative dermatitis
- Bullous dermatitis herpetiformis
- Severe seborrheic dermatitis
- Severe psoriasis
- Mycosis fungoides
- Urticaria

- *Allergic states*

Control of severe or incapacitating allergic conditions intractable to adequate trials of conventional treatment in:
- Bronchial asthma
- Contact dermatitis
- Atopic dermatitis
- Serum sickness
- Seasonal or perennial allergic rhinitis
- Drug hypersensitivity reactions
- Urticarial transfusion reactions
- Acute non-infectious laryngeal edema (epinephrine is the drug of first choice)

- *Ophthalmic diseases*

Severe acute and chronic allergic and inflammatory processes involving the eye, such as:
- Herpes zoster ophthalmicus
- Iritis, iridocyclitis
- Chorioretinitis
- Diffuse posterior uveitis and choroiditis
- Optic neuritis
- Sympathetic ophthalmia

- *Gastrointestinal diseases*

To tide the patient over a critical period of the disease in:
- Ulcerative colitis (systemic therapy)
- Regional enteritis (systemic therapy)

- *Respiratory diseases*
- Pulmonary sarcoidosis
- Berylliosis
- Fulminating or disseminated pulmonary tuberculosis when used concurrently with appropriate antituberculous chemotherapy
- Loeffler's syndrome not manageable by other means
- Aspiration pneumonitis

- *Edematous states*

To induce diuresis or remission of proteinuria in the nephrotic syndrome, without uremia, of the idiopathic type or that due to lupus erythematosus.

Immunosuppressive treatment

- *Organ transplantation*

Treatment of hematological and oncological disorders

- *Hematologic disorders*

- Acquired (autoimmune) hemolytic anemia
- Idiopathic thrombocytopenic purpura in adults (intravenous only; intramuscular administration is contraindicated)
- Secondary thrombocytopenia in adults
- Erythroblastopenia (R.B.C. anemia)
- Congenital (erythroid) hypoplastic anemia

- *Oncological diseases*

For palliative management of:

- Leukemias and lymphomas in adults
- Acute leukemia of childhood

Others

- Nervous system
  - Cerebral edema from tumor - primary or metastatic and/or associated with surgical or radiation therapy
  - Acute exacerbations of multiple sclerosis
  - Acute spinal cord injury. The treatment should begin within eight hours of injury.
- Tuberculous meningitis with subarachnoid block or impending block when used concurrently with appropriate antituberculous chemotherapy
- Trichinosis with neurological or myocardial involvement
- Prevention of nausea and vomiting associated with cancer chemotherapy

Endocrine disorders

- Primary or secondary adrenocortical insufficiency
- Acute adrenocortical insufficiency
  For these indications, the drugs of choice are hydrocortisone or cortisone. Synthetic analogues can be used in certain circumstances if they are combined with mineralocorticoids.
- Treatment of shock conditions: shock resulting from adrenocortical insufficiency or shock that does not respond to conventional treatment, in the case of confirmed or suspected adrenocortical insufficiency (in general, hydrocortisone is the preparation of choice. If mineralocorticoid effects are undesired, preference can be given to methylprednisolone).
- Prior to surgical procedures and in the case of severe disease or injury, in patients with known adrenocortical insufficiency or doubtful adrenal reserves.
- Congenital adrenal hyperplasia
- Non-suppurative thyroiditis
- Hypercalcaemia associated with cancer

4.2 Posology and method of administration

Posology – see table below for recommended dosages.

Table 1: Recommended dosages of methylprednisolone sodium succinate

As adjunctive therapy in life-threatening conditions	The recommended dose is 30 mg/kg, given intravenously over a period of at least 30 minutes. This dose may be repeated in the hospital every 4 to 6 hours for 48 hours depending on the clinical necessity (see section “Special warnings and precautions for use”).
"PULSE-THERAPY"	Suggested schedules:

Rheumatic disorders unresponsive to standard therapy of nonsteroidal anti-inflammatory drugs, gold salts and penicillamine (or during exacerbation episodes).	– Rheumatoid arthritis: – 1 g/day intravenous for 1, 2, 3 or 4 days or – 1 g/month intravenous for 6 months. As high doses of corticosteroids can cause an arrhythmogenic event, this therapy should be restricted to hospitals, which dispose of an electrocardiograph and defibrillator. The regimen should be administered over at least 30 minutes. The regimen may be repeated based on the patient's condition or if improvement has not occurred within a week after therapy.
Prevention of nausea and vomiting associated with cancer chemotherapy	Suggested schedules: – Mild to moderately emetogenic chemotherapy: Administer 250 mg intravenous over at least 5 minutes one hour before chemotherapy, at the initiation of chemotherapy and at the time of discharge from hospital. A chlorinated phenothiazine may also be used with the first dose for increased effect. – Severely emetogenic chemotherapy: Administer 250 mg intravenous over at least 5 minutes with appropriate doses of metoclopramide or a butyrophenone one hour before chemotherapy, then 250 mg intravenous at the initiation of chemotherapy and at the time of discharge from hospital.
Acute spinal cord injury	**The treatment should begin within eight hours of injury.** <u>For patients initiated on treatment within 3 hours of injury:</u> Administer 30 mg/kg as an IV bolus over a 15-minute period under continuous medical supervision, followed by a 45-minute pause, and then a continuous IV infusion of 5.4 mg/kg/hr for 23 hours. <u>For patients initiated on treatment within 3 to 8 hours of injury:</u> Administer 30 mg/kg as an IV bolus over a 15-minute period under continuous medical supervision, followed by a 45-minute pause, and then a continuous IV infusion of 5.4 mg/kg/hr for 47 hours. For the infusion pump, one should preferably choose another intravenous site than for the bolus injection. <u>This rate of bolus injection can only be used in this indication</u>, under the availability of ECG-monitoring and defibrillator. The administration of a high dose of methylprednisolone in bolus intravenously (doses of more than 500 mg over a period of less than 10 minutes) may cause arrhythmias, circulatory collapse and cardiac arrest.
In other indications	Initial dose will vary from 10 to 500 mg IV, depending on the clinical condition. Larger doses may be required for short-term management of severe, acute conditions such as bronchial asthma, serum sickness, urticarial transfusion reactions and acute exacerbations of multiple sclerosis. Initial doses up to 250 mg should be administered intravenously over a period of at least 5 minutes, while larger doses should be administered over at least 30 minutes. Subsequent doses may be administered intravenously or intramuscularly at intervals based on patient's response and clinical

	condition. Corticosteroid therapy is an adjunct to, and not replacement for, conventional therapy.

Dosage must be decreased or discontinued gradually when the drug has been administered for more than a few days. If a period of spontaneous remission occurs in a chronic condition, treatment should be discontinued. Routine laboratory studies, such as urinalysis of blood glucose 2 hours after meal, blood pressure, body weight and chest X-ray should be made at regular intervals during prolonged therapy. Upper GI X-rays are desirable in patients with an ulcer history or significant dyspepsia.
Medical surveillance is also needed in case of interruption of chronic treatment.
To administer by intravenous (or intramuscular) injection, prepare solution as directed.

Paediatric population
Dosage can be reduced for infants and children, but should be more influenced by the severity of the condition and response to therapy than by the patient's age or weight. It should not be less than 0.5 mg per kg every 24 hours.

Method of administration
The solution of sodium succinate of methylprednisolone may be administered by intravenous or intramuscular injection or by intravenous infusion. Intravenous injection is preferable for commencing treatment in cases of emergency.

4.3 Contraindications

Systemic fungal infections.
Hypersensitivity to methylprednisolone or to any of the excipients.
For use by the intrathecal route of administration.
For use by the epidural route of administration.
Methylprednisolone sodium succinate 40 mg presentations include lactose monohydrate produced from cow's milk. These presentations are therefore contraindicated in patients with a known or suspected allergy to cow's milk or its components or other dairy products because they may contain trace amounts of milk ingredients.

RELATIVE CONTRAINDICATIONS
Special risk groups:
Patients belonging to the following special risk groups should be under strict medical surveillance and should be treated during an as short as possible period (see also sections "Special warnings and precautions for use" and "Adverse reactions"): Children, diabetics, hypertensive patients, patients with psychiatric antecedents, certain infectious diseases, such as tuberculosis or certain viral diseases such as herpes and herpes zoster associated with ocular symptoms.

4.4 Special warnings and precautions for use

- Special risk groups
  Patients belonging to the following special risk groups should be under strict medical surveillance and should be treated during an as short as possible period.
  - Children: growth may be suppressed in children receiving long-term, daily-divided doses glucocorticoid therapy. The use of such a regimen should be restricted to those most serious indications.
  - Diabetics: manifestations of latent diabetes mellitus or increased requirements for insulin or oral hypoglycemic agents.
  - Hypertensive patients: aggravation of arterial hypertension.
  - Patients with psychiatric antecedents: existing emotional instability or psychotic

tendencies may be aggravated by corticosteroids.

- Since complications of treatment with glucocorticoids are dependent on the size of the dose and the duration of treatment, a risk/benefit decision must be made in each individual case as to dose and duration of treatment and as to whether daily or intermittent therapy should be used.
- In patients on corticosteroid therapy subjected to unusual stress, increased dosage of rapidly acting corticosteroids before, during and after the stressful situation is indicated.
- Glucocorticosteroids may mask some signs of infection and new infections may appear during their use. There may be decreased resistance and inability to localize infection when corticosteroids are used. Infections due to bacteria, viruses, fungi, protozoa or worms, in any part of the body, may be associated with the use of corticosteroids either alone or in combination with other immunosuppressive agents that affect cellular immunity, humoral immunity or neutrophil action. These infections can be moderate, severe and occasionally fatal. As the corticosteroid dose increases, more infections occur.
- Administration of live or live-attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of corticosteroids. Killed or inactivated vaccines may be administered to these patients; however, the therapeutic reaction to these vaccines may be diminished. Patients on non-immunosuppressive doses of corticosteroids may undergo any required immunisation procedures.
- Data from a clinical study conducted to establish the efficacy of methylprednisolone sodium succinate in septic shock, suggest that a higher mortality occurred in subsets of patients who entered the study with elevated serum creatinine levels or who developed a secondary infection after therapy began.
- The use of methylprednisolone sodium succinate in active tuberculosis should be restricted to those cases of fulminating or disseminated tuberculosis, where appropriate anti-tuberculosis regimen is initiated simultaneously.
- If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur. During prolonged corticosteroid therapy, these patients should receive chemoprophylaxis.
- Because rare instances of anaphylactic (e.g., bronchospasm) reactions have occurred in patients receiving parenteral corticosteroid therapy, appropriate precautionary measures should be taken prior to administration, especially when the patient has a history of allergy to any drug.
- Drug-induced secondary adrenocortical insufficiency may be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstituted. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently.
- There is an enhanced effect of glucocorticosteroids on patients with hypothyroidism and in those with cirrhosis.
- Severe medical events have been reported in association with the intrathecal/epidural routes of administration (see section “Undesirable effects”).
- Corticosteroids should be used cautiously in patients with ocular herpes simplex because of possible corneal perforation.
- Corticosteroids should be used with caution in non-specific ulcerative colitis if there is a risk of impending perforation, abscess or other pyogenic infections, diverticulitis, fresh intestinal anastomoses, active or latent gastric or peptic ulcer, renal insufficiency, hypertension, osteoporosis or myasthenia gravis.
- Thrombosis including venous thromboembolism has been reported to occur with corticosteroids. As a result corticosteroids should be used with caution in patients who have or may be predisposed to thromboembolic disorders.
- Growth and development of infants and children on prolonged corticosteroid therapy should be carefully observed.
- Hepatobiliary effects: drug induced liver injury including acute hepatitis or liver enzyme

increase can result from cyclical pulsed intravenous methylprednisolone (usually at initial dose ≧1 g/day). Rare cases of hepatotoxicity have been reported. The time to onset can be several weeks or longer. In the majority of case reports resolution of the adverse events has been observed after treatment was discontinued. Therefore, appropriate monitoring is required.

- Convulsions have been observed during combined treatment with methylprednisolone and cyclosporine. Since concurrent administration of these two products results in mutual inhibition of metabolism, convulsions and other adverse effects due to the individual use of these products may be more likely to occur.
- Acute myopathy has been reported with the use of high corticosteroid doses, usually in patients with disorders of neuromuscular transmission (for example, myasthenia gravis), or in patients receiving concurrent treatment with neuromuscular blockers (for example, pancuronium). This acute myopathy is generalized, can affect eye muscles and respiratory muscles and can result in quadriparesis. Increased creatine kinase levels can occur. After discontinuation of the corticosteroid treatment it may take weeks to years before clinical improvement or recovery occurs.
- Kaposi's syndrome has been reported in patients receiving corticosteroid treatment. Discontinuation of corticosteroid treatment may result in clinical remission.
- An attack of pheochromocytoma, which can be fatal, was reported after administration of systemic corticosteroids. Corticosteroids may only be administered to patients with suspected or identified pheochromocytoma after an appropriate assessment of benefits/risks.
- All presentations contain benzyl alcohol. Benzyl alcohol has been reported to be associated with a fatal "gasping syndrome" (respiratory disorder characterized by a persistent gasping for breath) in premature infants. Benzyl alcohol must not be administered to premature or full-term new-borns. It may cause toxic reactions and anaphylactoid-type reactions in infants and children up to 3 years old.
- Cow's milk allergy – Solu-Medrol 40 mg

  Solu-Medrol 40mg contains lactose monohydrate produced from bovine origin as an excipient and may therefore contain trace amounts of cow's milk proteins (the allergens of cow's milk). Serious allergic reactions, including bronchospasm and anaphylaxis, were reported in patients allergic to cow's milk proteins who were treated for acute allergic conditions. Patients with known or suspected allergy to cow's milk must not be administered Solu-Medrol 40mg (see section 4.3).

  Allergic reactions to cow's milk proteins should be considered in patients receiving Solu-Medrol 40mg for the treatment of acute allergic conditions in whom symptoms worsen or who are presenting new allergic symptoms (see section 4.3). Administration of Solu-Medrol 40mg should be stopped, and the patient's condition should be treated accordingly.
- Solu-Medrol 40mg contains lactose. Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.
- Corticotherapy has to be considered when interpreting a whole series of biological tests and parameters (e.g., skin tests, thyroid hormone levels).
- The duration of the treatment should in general be kept as short as possible. Medical surveillance is recommended during chronic treatment (see also Posology and method of administration). The discontinuation of a chronic treatment should also occur under medical surveillance (gradual discontinuation, evaluation of the adrenocortical function). The most important symptoms of adrenocortical insufficiency are asthenia, orthostatic hypotension and depression.
- Injection into the deltoid muscle should be avoided because of the high incidence of subcutaneous atrophy.
- Methylprednisolone sodium succinate should not be used routinely to treat head injury as

demonstrated by the results of a multicenter study. The study results revealed an increased mortality in the 2 weeks after injury in patients administered methylprednisolone sodium succinate compared to placebo (1.18 relative risk). A causal association with methylprednisolone sodium succinate treatment has not been established.

- Co-treatment with CYP3A inhibitors, including cobicistat-containing products, is expected to increase the risk of systemic side effects. The combination should be avoided unless the benefit outweighs the increased risk of systemic corticosteroid side effects, in which case patients should be monitored for systemic corticosteroid side effects (see section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

DESIRED INTERACTIONS

- Prevention of nausea and vomiting associated with cancer chemotherapy.
  - Mild to moderately emetogenic chemotherapy.

  For an increased effect, a chlorinated phenothiazine may be used with the first dose methylprednisolone (one hour before chemotherapy).
  - Severely emetogenic chemotherapy.

  For an increased effect, metoclopramide or a butyrophenone may be used with the first dose methylprednisolone (one hour before chemotherapy).
- By the treatment of fulminating or disseminated pulmonary tuberculosis and tuberculous meningitis with subarachnoid block or impending block, methylprednisolone is used concurrently with appropriate antituberculous chemotherapy.
- By the treatment of neoplastic diseases like leukemia and lymphoma, methylprednisolone is usually used in conjunction with an alkylating agent, an antimetabolite and a vinca-alkaloid.

UNDESIRED INTERACTIONS

- Combination of glucocorticosteroids with ulcerogenic drugs (e.g., salicylates and NSAIDs) increases the risk of gastrointestinal complications.
- Combination of glucocorticosteroids with thiazide-diuretics increases the risk of glucose intolerance.
- Glucocorticosteroids can increase the requirements for insulin or oral hypoglycemic agents in diabetics.
- While on corticosteroid therapy, patients should not be vaccinated against smallpox. Other immunization procedures should not be undertaken in patients who are on corticosteroids, especially on high doses, because of possible hazards of neurological complications and lack of antibody response.
- Acetylsalicylic acid should be used cautiously in conjunction with corticosteroids in hypoprothrombinemia. Methylprednisolone can increase the clearance of chronic high doses of aspirin. This may result in a drop in salicylate serum levels or an increased risk of salicylate toxicity when the administration of methylprednisolone is discontinued.
- Convulsions have been reported with concurrent use of methylprednisolone and cyclosporine. Concurrent administration of these agents results in a mutual inhibition of metabolism. Therefore, it is possible that convulsions and other adverse events associated with the individual use of either drug may be more apt to occur.
- Drugs that induce hepatic enzymes (such as phenobarbital, phenytoin and rifampicin) can increase the clearance of methylprednisolone. It may be necessary to increase the dosage of methylprednisolone in order to obtain the desired response.
- CYP3A4-inhibitors (such as macrolides, triazole antimycotics and some calcium channel blockers) can inhibit the metabolism of methylprednisolone and therefore, reduce its clearance. In order to avoid steroid toxicity, the dosage of methylprednisolone should therefore be titrated.
- Protease inhibitors (e.g. ritonavir, indinavir) and pharmacokinetic enhancers (e.g.,

cobicistat) inhibit CYP3A4 activity leading to a decreased hepatic clearance and increased plasma concentration of the corticosteroid. A dose adjustment of the corticosteroid may be required (see section 4.4).

– The effect of methylprednisolone on oral anticoagulants varies. Both increased and decreased effects of the anticoagulant have been reported when it is combined with corticosteroids. Consequently, coagulation parameters should be monitored in order to achieve the desired anticoagulant effect.

4.6 Fertility, pregnancy and lactation

Some animal studies have shown that corticosteroids when administered during pregnancy at high doses, may cause fetal malformations. Administration of corticosteroids in pregnant women however does not appear to induce congenital anomalies. One retrospective study revealed an increased incidence in low birth weight in infants whose mothers had received corticosteroids. Despite the results in animal experiments, the risk of fetal lesions is low when the drug is used during pregnancy. Since studies in humans cannot exclude the risk of lesions, methylprednisolone sodium succinate should only be used in pregnancy if it is strictly necessary.

If a chronic treatment with corticosteroids has to be stopped during pregnancy (as with other chronic treatments), this should occur gradually (see also Posology and method of administration). In some cases (e.g., substitution treatment of adrenocortical insufficiency) however, it can be necessary to continue treatment or even to increase dosage. Corticosteroids readily cross the placenta. Though neonatal adrenocortical insufficiency is rare in infants who were exposed *in utero* to corticosteroids, infants who were exposed to substantial doses of corticosteroids should be carefully observed and evaluated for signs of adrenocortical insufficiency. In case of labor and delivery, no effects are known. Corticosteroids, including prednisolone, are excreted in breast milk.

4.7 Effects on ability to drive and use machines

Although visual disorders belong to the rare adverse reactions, caution is recommended in patients driving cars and/or using machines.

4.8 Undesirable effects

The following adverse reactions have been reported with the following contraindicated routes of administration: Intrathecal/Epidural: Arachnoiditis, functional gastrointestinal disorder/bladder dysfunction, headache, meningitis, paraparesis/paraplegia, convulsions, sensory disturbances. The frequency of these adverse reactions is not known.

Systemic adverse reactions may be observed. Although rarely occurring in very short term therapy, they should always be carefully traced. This is part of the follow-up of any corticotherapy, and does not specifically pertain to any particular product. These possible adverse reactions of glucocorticoids like methylprednisolone are:

Infections and infestations: masking of infections, activation of latent infections, opportunistic infections.

Immune system disorders: hypersensitivity reactions (including anaphylaxis, with or without circulatory collapse, cardiac arrest, bronchospasm).

Endocrine disorders: development of Cushingoid state, suppression of the pituitary adrenocortical axis.

Metabolism and nutrition disorders: sodium retention, fluid retention, hypokalemic alkalosis, decreased carbohydrate tolerance, manifestations of latent diabetes mellitus, increased requirements for insulin or oral hypoglycemic agents in diabetics. In comparison with cortisone or hydrocortisone, mineralocorticoid effects are less likely to occur with synthetic derivatives as methylprednisolone. Dietary salt restriction and potassium supplementation may be necessary. All glucocorticosteroids increase calcium excretion. Epidural lipomatosis (frequency unknown).

Blood and lymphatic system disorders: leukocytosis (frequency unknown).

Psychiatric disorders: Psychic derangements ranging from euphoria, insomnia, mood swings, personality changes and severe depression to frank psychotic manifestations.

Nervous system disorders: increased intracranial pressure with papillary edema (pseudotumor cerebri), seizures, vertigo.

Eye disorders: posterior subcapsular cataracts, exophthalmos. Chorioretinopathy (frequency unknown).

Prolonged use of glucocorticoids may produce, glaucoma with possible damage to the optic nerves and may enhance the establishment of secondary ocular infections due to fungi or viruses.

Glucocorticoids should be used cautiously in patients with ocular herpes simplex for fear of corneal perforation.

Cardiac disorders: congestive heart failure in susceptible patients, myocardial rupture after myocardial infarction, arrhythmias.

There are reports or cardiac arrhythmias and/or circulatory collapse and/or cardiac arrest following the rapid administration of large intravenous doses of methylprednisolone sodium succinate (greater than 0.5 g administered over a period of less than 10 minutes). Bradycardia has been reported during or after the administration of large doses of methylprednisolone sodium succinate and may be unrelated to the speed or duration of infusion. After administration of high doses of glucocorticoids, also tachycardia has been reported.

Vascular disorders: hypertension, hypotension, petechiae. Thrombotic events (frequency unknown).

Respiratory, thoracic and mediastinal disorders: persistent hiccups with high corticosteroid doses.

Gastrointestinal disorders: peptic ulceration with possible subsequent perforation and hemorrhage, gastric hemorrhage, pancreatitis, esophagitis, intestinal perforation.

Hepatobiliary disorders: hepatitis, increase of liver enzymes (for example: SGOT, SGPT. The frequency of this effect is unknown).

Skin and subcutaneous tissue disorders: ecchymoses, thin fragile skin. Repeated local subcutaneous injections may cause local cutaneous atrophy.

Musculoskeletal and connective tissue disorders: steroid myopathy, muscle weakness, osteoporosis, aseptic necrosis

Reproductive system and breast disorders: menstrual irregularities.

General disorders and administration site conditions: impaired wound healing, suppression of growth in children.

Investigations: potassium loss, possible transient and moderate increase of alkaline phosphatase levels but it is not associated with any clinical syndrome, negative nitrogen balance due to protein catabolism, increased intraocular pressure, suppression of reactions to skin tests.

Injury, poisoning and procedural complications: pathologic fractures, vertebral compression fractures, tendon rupture (mainly the Achilles' tendon).

4.9 Overdose

There is no clinical syndrome of acute overdosage with methylprednisolone sodium succinate. Chronic overdosage induces typical Cushing symptoms. Methylprednisolone is dialyzable.

5. PHARMACOLOGICAL PROPERTIES

This product is an intramuscular and intravenous injectable form of methylprednisolone, a synthetic glucocorticosteroid. This highly concentrated aqueous solution is particularly suitable for the treatment of pathologic conditions, in which an effective and rapid hormonal effect is required. Methylprednisolone has a strong anti-inflammatory, immunosuppressive and anti-allergic activity.

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: glucocorticosteroid, ATC H02A B04

Glucocorticoids diffuse across cell membranes and complex with specific cytoplasmic receptors. These complexes then enter the cell nucleus, bind to DNA (chromatin), and stimulate transcription of mRNA and subsequent protein synthesis of various enzymes thought to be ultimately responsible for the numerous effects of glucocorticoids after systemic use. Glucocorticoids not only have an important influence on inflammatory and immune processes, but also affect the carbohydrate, protein and fat metabolism. They also act on the cardiovascular system, the skeletal muscles and the central nervous system.

- Effect on the inflammatory and immune process:
  The anti-inflammatory, immunosuppressive and anti-allergic properties of glucocorticoids are responsible for most of the therapeutic applications. These properties lead to the following results:
  - reduction of the immunoactive cells near the inflammation focus;
  - reduced vasodilation;
  - stabilization of the lysosomal membranes;
  - inhibition of phagocytosis;
  - reduced production of prostaglandins and related substances.

  A dose of 4 mg methylprednisolone has the same glucocorticosteroid (anti-inflammatory) effect as 20 mg hydrocortisone. Methylprednisolone has only a minimal mineralocorticoid effect (200 mg methylprednisolone are equivalent to 1 mg desoxycorticosterone).
- Effect on carbohydrate and protein metabolism:
  Glucocorticoids have a protein catabolic action. The liberated amino acids are converted into glucose and glycogen in the liver by means of the gluconeogenesis process. Glucose

absorption in peripheral tissues decreases, which can lead to hyperglycemia and glucosuremia, especially in patients who are prone to diabetes.

– Effect on fat metabolism:
  Glucocorticoids have a lipolytic action. This lipolytic activity mainly affects the limbs. They also have a lipogenetic effect which is most evident on chest, neck and head. All this leads to a redistribution of the fat deposits.

Maximum pharmacologic activity of corticosteroids lags behind peak blood levels, suggesting that most effects of the drugs result from modification of enzyme activity rather than from direct actions by the drugs.

5.2 Pharmacokinetic properties

In vivo, cholinesterases rapidly hydrolyze methylprednisolone sodium succinate to free methylprednisolone.

In man, methylprednisolone forms a weak dissociable bond with albumin and transcortin. Approximately 40% to 90% of the drug is bound.

Intravenous infusions with 30 mg/kg, administered over 20 minutes or 1 g administered over 30 to 60 minutes lead after approximately 15 minutes to peak methylprednisolone plasma levels of nearly 20 µg/ml. About 25 minutes after an intravenous bolus injection of 40 mg peak methylprednisolone plasma values of 42-47 µg/100 ml are measured. Intramuscular injections of 40 mg give peak methylprednisolone plasma levels of 34 µg/100 ml after some 120 minutes. Intramuscular injections give lower peak values than intravenous injections. With intramuscular injections plasma values persist for a longer period, with the result that both administration patterns lead to equivalent quantities of methylprednisolone. The clinical importance of these small differences is probably minimal when we consider the mechanism of action of glucocorticoids.

A clinical response is usually observed 4 to 6 hours after administration. In the treatment of asthma, the first beneficial results can already be perceived after 1 or 2 hours. The plasma half-life of methylprednisolone sodium succinate is 2.3 to 4 hours and appears to bear no relation to the administration pattern.

Methylprednisolone is a glucocorticoid with a medium-term activity. It has a biological half-life of 12 to 36 hours. The intracellular activity of glucocorticoids results in a clear difference between plasma half-life and pharmacological half-life. Pharmacological activity persists after measurable plasma levels have disappeared. The duration of anti-inflammatory activity of glucocorticoids approximately equals the duration of hypothalamic-pituitary-adrenal (HPA) axis suppression.

Metabolism of methylprednisolone occurs via hepatic routes qualitatively similar to that of cortisol. The major metabolites are 20 beta-hydroxymethylprednisolone and 20 beta-hydroxy-6 alpha-methylprednisone. The metabolites are mainly excreted in the urine as glucuronides, sulfates and unconjugated compounds.

Following intravenous administration of ^{14}C labeled methylprednisolone, 75% of the total radioactivity was recovered in the urine in 96 hours, 9% was recovered in human feces after 5 days and 20% in the bile.

6. PHARMACEUTICAL PARTICULARS

6.1 Incompatibilities

Intravenous compatibility and stability of methylprednisolone sodium succinate solutions and with other drugs in intravenous admixtures are dependent on admixture pH, concentration, time, temperature and the ability of methylprednisolone to solubilize itself. Thus, to avoid compatibility and stability problems, whenever possible it is recommended that solutions of methylprednisolone sodium succinate be administered separate from other drugs and as either intravenous push, through and intravenous medication chamber or as an intravenous "piggy-back" solution.

6.2 Special precautions for storage

Please refer to the outer container for the storage condition.

6.3 Special precautions for disposal and other handling

DIRECTIONS FOR USE OF THE ACT-O-VIAL

1. Press down on plastic activator to force diluent into the lower compartment.
2. Gently agitate to effect solution.
3. Remove plastic covering center of stopper.
4. Sterilize the released part of the rubber stopper.
5. Insert needle, preferably a 22G, vertically through center of stopper until tip is just visible. Turn the vial and draw up the required dose. If a thicker needle is used, it is important to avoid to turn the needle and to insert it perpendicularly to the center of rubber stopper.

DIRECTIONS FOR USE OF THE VIAL
Under aseptic conditions add the diluent to the vial with sterile powder. Do only use the special diluent.

To withdraw the dose from the vial, please refer to point 5 “Directions for use of the Act-O-Vial” regarding the size of the needle to be preferably used.

PREPARATION OF PERFUSION SOLUTIONS
First reconstitute the solution as directed. Therapy may be initiated by administering the methylprednisolone sodium succinate solution intravenously over a period of at least 5 minutes (e.g., doses up to and including 250 mg) to at least 30 minutes (e.g., doses exceeding 250 mg). Subsequent doses may be withdrawn and administered similarly. If desired, the medication may be administered in dilute solutions by admixing the reconstituted product with dextrose 5% in water, normal saline, dextrose 5% in 0.45% or 0.9% sodium chloride. The resulting solutions are physically and chemically stable for 48 hours.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

August 2017
Hong Kong